comprises culturing the cell of claim 63 under conditions that permit expression of the human PAMP.

REMARKS

This submission is in response to the Official Action dated June 12, 2002. Claims 1-6, 18-28, 30, 46, 48, 51, 55, 62 and 64 have been cancelled. Claims 47, 49, 50, 52-54, 56, 59, 60, 63 and 65 have been amended.

Thus, claims 47, 49, 50, 52-54, 56-61 and 63 are pending and at issue.

The amendments are made without admission and without prejudice to applicant's right to pursue the cancelled subject matter in this or another patent application. Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

Claim 47 has been amended to independent form, and to recite that the isolated nucleic acid encodes the human PAMP (SEQ ID NO:14). This amendment is supported by the specification, for example by original claims 2-3 and 7, Figures 1A and 1B, and page 36, line 26 to page 37 line 27.

Claim 52 has been amended to independent form, and to recite that the isolated cell is transfected with a vector comprising a nucleic acid encoding a function-conservative variant of human PAMP having at least 60% amino acid identity to SEQ ID NO:14. The term "function-conservative" is well-known in the art and is further defined in the specification at page 17, lines 20-24.

Claim 54 has been amended to recite a method for producing a function-conservative variant of human PAMP. Support for this amendment can be found in the specification, for example at page 10, lines 19-26.

Claim Objections

Claims 46, 48, 52, 53, 60 and 61 have been objected to for allegedly being drawn to a non-elected invention. The Examiner has stated that the Applicants have elected examination of the human PAMP (paper number 10) while the claims recite PAMP from other organisms.

Claims 46 and 48 have been cancelled, thus obviating this objection. Claims 52, 53, 60 and 61 have been amended to recite human PAMP or the coding sequence of human PAMP. Accordingly, this objection has been overcome and should be withdrawn.

Priority

The Examiner has maintained his contention that the claims relating to human PAMP sequences are not entitled to the priority of provisional application serial no. 60/127,542.

Applicants respectfully disagree. The human PAMP amino acid sequence described in the priority application (SEQ ID NO:2), includes the entire human PAMP amino acid sequence of the instant application (SEQ ID NO:14). The human PAMP

nucleotide sequence in the priority application (SEQ ID NO:1) also includes the entire coding sequence for human PAMP.[1] While SEQ ID NO:13 also comprises additional untranslated regions, however, these are not part of the coding sequence. It is therefore clear that Applicants were in possession of the claimed PAMP nucleotide and amino acid sequences in the priority application, in view of the explicit written description of them in the priority application.

Claim Rejections - 35 U.S.C. 112

Written Description

Claims 51, 54, 55, 59-62 and 65 have been rejected as allegedly failing to meet the written description requirement. In particular, the Examiner contends that (1) the specification does not describe the relevant identifying characteristics of all of the nucleic acid sequences, or of the encoded proteins which uniquely define the sequences as a PAMP, and (2) that one could not determine if a sequence derived from another protein would be considered a PAMP because a function for PAMP is not

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[1] In the previous Response to Office Action, Applicants' attorney stated that SEQ ID NO:1 in the priority application "includes almost the entire coding region" of SEQ ID NO:13. (See Response to Office Action filed 1/23/2002, page 8, 2nd paragraph). This sentence should have read "includes the entire coding region, and almost the entire non-coding region." The inventors have informed the undersigned that "additional DNA was added to the untranslated region which was included in the final application." Applicant's attorney apologizes for any confusion this mistake may have caused.

described.

The applicants respectfully disagree. As amended, the claims recite nucleic acids encoding PAMP proteins characterized by their capability to bind to presenilins, thus providing a functional feature of PAMP, and by being function-conservative variants having at least 60% amino acid identity to SEQ ID NO:14, thus providing structural features.

Claims 51, 55 and 62 have been cancelled, thus obviating the rejection of these claims.

Claim 52 has been amended to recite a cell transfected with a vector comprising a nucleic acid encoding a function-conservative variant of human PAMP having at least 60% amino acid identity to SEQ ID NO:14, and claim 54, as amended, recites a method for producing a function-conservative variant of human PAMP, comprising culturing the cell of claim 52.

Function-conservative variants are defined in the specification on page 17, lines 8-24, as follows:

> "Function-conservative variants" are those in which a given amino acid residue in a protein or enzyme has been changed without altering the overall conformation and function of the polypeptide, including, but not limited to, replacement of an amino acid with one having similar properties (such as, for example, polarity, hydrogen bonding potential, acidic, basic, hydrophobic, aromatic, and the like). Amino acids with similar properties are well known in the art. For example, arginine, histidine and lysine are hydrophilic-basic

> amino acids and may be interchangeable. Similarly, isoleucine, a hydrophobic amino acid, may be replaced with leucine, methionine or valine. Such changes are expected to have little or no effect on the apparent molecular weight or isoelectric point of the protein or polypeptide. Amino acids other than those indicated as conserved may differ in a protein or enzyme so that the percent protein or amino acid sequence similarity between any two proteins of similar function may vary and may be, for example, from 70% to 99% as determined according to an alignment scheme such as by the Cluster Method, wherein similarity is based on the MEGALIGN algorithm. A "function-conservative variant" also includes a polypeptide or enzyme which has at least 60 % amino acid identity as determined by BLAST (Altschul SF, *et al.*, J Mol Biol 1990; 215: 403-410) or FASTA algorithms, preferably at least 75%, most preferably at least 85%, and even more preferably at least 90%, and which has the same or substantially similar properties or functions as the native or parent protein or enzyme to which it is compared.

The specification provides eight human PAMP variants, several of which have at least 60% amino acid identity to SEQ ID NO:14, for example, on page 43, line 24 to page 44, line 4. Accordingly, the Examiner's first contention recited above is obviated, since the claimed nucleic acids are characterized by encoding function-conservative variants of SEQ ID NO:14 having at least 60% sequence identity to SEQ ID NO:14.

With respect to the Examiner's second concern, the functionality of human PAMP, the specification describes functional PAMP variants. Specifically, Example 2 describes assaying a number of PAMP variants for their interaction with

presenilins. In this Example, capability of interacting with PAMP was evaluated by co-immunoprecipitation of PAMP and presenilin 1 (see, *e.g.*, pages 44-46), thus identifying the specific regions of PAMP involved in the presinilin interaction to evaluate PAMP functionality, *i.e.*, interaction with a presenilin, and functional human PAMP variants. Accordingly, claims 52 and 54, as amended herewith, clearly comply with the written description requirement.

Moreover, claim 59 has been amended to recite that the claimed vector comprises a nucleic acid encoding a mutant PAMP which has a mutation in one or more of a select group of amino acid residues of human PAMP (SEQ ID NO:14). This claim thereby contains both the functional features described above for claim 52, as well as specific structural features. Claims 60-65 depend from claim 59, thereby incorporating these structural features.

It follows that Applicants were in possession of the claimed invention at the time of filing of the application. Reconsideration and withdrawal of this rejection is respectfully requested.

Enablement

Claims 51, 54, 55, 59-62 and 65 have also been rejected as allegedly failing to comply with the enablement requirement. Specifically the Examiner contends that there is no enablement for any and all PAMP functional fragments or mutant

PAMP-encoding nucleic acids. It is noted that the Examiner has previously stated that the specification is enabling "for nucleic acids comprising a PAMP-encoding nucleic acid of SEQ ID NO:13 or nucleic acids encoding the amino acid sequence of SEQ ID NO:14." See June 12, 2002 Office Action at page 7, paragraph 2.

It is respectfully submitted that the invention, as set forth by the amended claims, is enabled.

Claims 51, 55 and 62 have been cancelled, thus obviating the rejection of these claims. Claim 52, as amended, recites a cell transfected with a vector comprising a nucleic acid encoding a function-conservative variant of human PAMP having at least 60% amino acid identity to SEQ ID NO:14. Claim 56, as amended, recites a nucleic acid encoding a mutant PAMP having a mutation in a specific amino acid residue of SEQ ID NO:14.

As discussed above, the specification, in particular Example 2 (pages 43-46), provides working examples of the preparation and evaluation of several human PAMP variants for PAMP functionality, *i.e.*, binding to a presenilin protein. In addition, comparison of amino acid sequences for evaluation of amino acid sequence identity is well known in the art, and facilitated by the available sequence databases and sequence evaluation programs described in the specification at, *e.g.*, page 17. The specification describes and enables nucleic acids, host cells, and nucleic acids for PAMP variants that might require some experimentation, but no undue or unreasonable

experimentation, for one of skill in the art.

Thus, withdrawal of the instant rejection based on §112 is respectfully requested.

Claim Rejections - 35 U.S.C. 102

Claims 51, 54, 55, 59-62 and 65 have been rejected under §102(b) as being anticipated by Genbank Accession Number D87442. The Examiner contends that D87442 discloses a nucleic acid encoding a functional fragment of a PAMP whose nucleic acid sequence is 99.9% identical to positions 145-2949 of SEQ ID NO:13 and reads on an isolated nucleic acid encoding a functional PAMP fragment and a mutant PAMP.

The applicants respectfully disagree. Claims 51, 55 and 62 have been cancelled, thus obviating the rejection of these claims. Claims 52, 54, 59-61 and 65 are directed to cells comprising a nucleic acid encoding a function-conservative variant of human PAMP having about 60% amino acid identity to SEQ ID NO:14, and methods for producing a variant of human PAMP by culturing such cells, as well as isolated nucleic acids encoding human PAMP variants having specific mutations in SEQ ID NO:14.

GenBank entry D87442 does not anticipate the claimed invention. This reference mentions nothing about a protein, much less a characteristic of the protein, interaction with presenilins, or production of proteins capable of such interaction by

culturing host cells transfected with a vector encoding such a protein. Further, there is no suggestion in the GenBank entry of mutants of this protein, any phenotype associated with such mutants, or the specific amino acids for such mutations, much the recited less mutations of SEQ ID NO:14 residues. Since an anticipatory reference must teach each and every aspect of the claimed invention either explicitly or impliedly (MPEP 706.02), the D87442 reference clearly does not anticipate the invention as set forth by the claims as amended herewith.

As for claims 52 and 54, it is respectfully submitted that GenBank entry D87442 does not disclose or suggest a cell transfected with a PAMP protein or methods to produce human PAMP variants using such cells, and, moreover, does not identify whether the sequence encodes a functional protein or is just a pseudogene. In fact, even if such cells were taught, this reference does not provide any incentive for including its sequence into a vector for expression by a host cell, nor identify any coding region, or, if there was such a coding region, where it would start. Since the D87442 entry thus fails to teach or suggest and thus does not enable cells comprising vectors encoding PAMP variants sequences recited in the claims, D87442 does not anticipate the invention in amended claims 52 and 54. Similarly, claims dependent thereon are also distinct from and therefore patentable over D87442.

It is therefore respectfully requested that the instant rejection based on §102 be withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is earnestly requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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Reply under 37 CFR 1.116 - Expedited Procedure
Examining Group 1632

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I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Peter H. ST. GEORGE-HYSLOP; Paul E. FRASER

Serial No.: 09/541,094 Art Unit: 1632

Confirmation No.: 4017

Filed: March 31, 2000 Examiner: J.T. Woitach

For: A NOVEL PRESENILIN ASSOCIATED MEMBRANE PROTEIN AND USES THEREOF

MARK-UP OF CLAIMS FOR AMENDMENT
PURSUANT TO 37 C.F.R. §1.121

September 12, 2002

Box AF
Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

47. (Amended) [The] An isolated nucleic acid [of claim 46,] which encodes human

presenilin-associated membrane protein (PAMP) (SEQ ID NO:14).

49. (Amended) The isolated nucleic acid of claim [48] 47, which comprises a nucleotide [the coding] sequence [of] encoding human PAMP (SEQ ID NO:13).

50. (Amended) A vector comprising the nucleic acid of claim [46] 47, operatively associated with an expression control sequence.

52. (Amended) [The] An isolated cell [of claim 51, wherein the] transfected with a vector, which vector comprises a nucleic acid [encodes] encoding a function-conservative variant of human PAMP having at least 60% amino acid identity to [(] SEQ ID NO: 14 [), mouse (SEQ ID NO:16), *D. melanogaster* (SEQ ID NO:18), or *C. elegans* (SEQ ID NO:12) PAMP] and being capable of interacting with a presenilin.

53. (Amended) The isolated cell of claim 52, wherein the nucleic acid comprises [the coding] a nucleotide sequence [of] encoding human PAMP (SEQ ID NO:13)[, mouse (SEQ ID NO: 15) *D. Melanogaster* (SEQ ID NO: 17), or *C. elegans* (SEQ ID NO: 11) PAMP].

54. (Amended) A method for producing a function-conservative variant of human PAMP, which method comprises culturing the cell of claim [51] 52 under conditions

that permit expression of the PAMP variant.

56. (Amended) [The] An isolated nucleic acid [of claim 55] encoding a mutant PAMP, wherein the mutant PAMP has a mutation in an amino acid residue corresponding to an amino acid selected from the group consisting of C230, D336, Y337, and both D336 and Y337, of human PAMP (SEQ ID NO:14).

59. (Amended) A vector comprising the nucleic acid of claim [55] 56, operatively associated with an expression control sequence.

60. (Amended) An isolated cell transfected with [a] the vector of claim 59 [comprising a nucleic acid encoding a mutant PAMP, and an expression control sequence operatively associated with said nucleic acid].

63. (Amended) The isolated cell of claim [62] 52, wherein the [nucleic acid encodes] human PAMP has SEQ ID NO: 14.

65. (Amended) A method for producing human PAMP, which method comprises culturing the cell of claim [62] 63 under conditions that permit expression of the human PAMP.